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| 10/664,725 | 09/18/2003 | Manabu Nakatani | 01-1395 | 4358 |

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| EXAMINER | |
|---|---|
| HELM, CARALYNNE E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1615 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO.e-Office.rdg@boehringer-ingelheim.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/664,725 | NAKATANI ET AL. | |
| | Examiner | Art Unit | |
| | CARALYNNE HELM | 1615 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 July 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,6-9 and 11-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6-9, and 11-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/18/11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 18, 2011 has been entered.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6-9, 11-12, and 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ambuhl et al. (previously cited) in view of Hauel et al. (previously cited)

Ambuhl et al. teach a tablet composition with a poorly soluble drug, a water soluble diluent and polyoxamer (see paragraph 8; instant claim 1). Specifically, they teach that the drug is included along with a polymer, surfactant, and carrier where the surfactant is envisioned as poloxamer 188 (also known as polyoxamer), and the water-soluble diluent (called a carrier by Ambuhl et al.) is envisioned as mannitol (see paragraphs 15, 44, 73-83, and 151; instant claims 6-8). Poloxamer 188 meets the molecular weight requirement for the polyoxamer. Ambuhl et al. also teach that these preparations have drug at 15% to 40%, water soluble diluent at 10% to 40%, and surfactant from 10% to 70% of the composition (see paragraph 56, 88, and 128; instant claims 1 and 14-15). A lubricant, such as magnesium stearate, is envisioned in the composition (see paragraphs 1121-122; instant claim 9). One method embodiment is performed by spraying a solution of the drug with surfactant onto a carrier that is then dried which is a process that is also known as fluid bed granulation (see paragraph 152; instant claim 14). In addition, Ambuhl et al. teach in another embodiment that the composition may be prepared by spray-drying a combination of the drug with surfactant in an aqueous solution (see paragraph 151 and 171-173; instant claim 15). The drug

particulate from either method is then combined with an outer tablet matrix that is composed of a water soluble diluent that includes lactose (see paragraph 186; instant claim 15). This outer matrix material can comprise 10% to 60% of the composition and contains 75% lactose, yielding a composition with 7.5% to 45% lactose (see paragraphs 187 and 189; instant claims 14-15). Each of these preparation techniques requires the active agent to be dissolved in a solution; however the envisioned drugs are poorly soluble in water. Ambuhl et al. do not explicitly teach the presence of a basic agent in the composition or telmisartan as the poorly water soluble drug.

Hauel et al. teach a collection of benzamidazole compounds as active agents where telmisartan is explicitly envisioned (see first listed compound in claim 6). They go on to teach dosage forms for administration of the compounds and tablet formulations with 50 mg or 100 mg doses are included (see examples III-V; instant claims 10-12). Hauel et al. teach a preference for the benzamidazole compounds, which like telmisartan have a carboxyl functional group (see page 113 lines 1-4). Telmisartan was known to be solubilized by strong base. Hauel et al. demonstrate this solubility in example II where a solution of their envisioned active is prepared by combination with meglumine (also known as methyl glucamine) and water where the active and meglumine are each present at 0.2 moles (1:1 molar ratio; see instant claims 1 and 14-15).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use telmisartan as the poorly soluble drug in the methods taught by Ambuhl et al. because it was a poorly water soluble drug known at the time of the invention and

it was also envisioned in tablets utilizing many of the same components taught by Ambuhl et al. (e.g. The composition in example V taught by Hauel et al. falls within the set taught by Ambuhl et al.). Since the highlighted methods of making such a composition require the drug to be solubilized and Hauel et al. teach that their compounds can be solubilized by combination with meglumine, it would have been obvious to include meglumine at a 1:1 molar ratio in the spray drying or granulating solution taught by Ambuhl et al. to insure the drug's presence in dissolved form. This modification then yields the tablets of Ambuhl et al. with mannitol as water soluble diluent at 10% to 40% or lactose as water soluble diluent at 7.5% to 45%, poloxamer 188 as the surfactant at 10% to 70%, telmisartan at 15% to 40%, and the basic agent meglumine at a 1:1 molar ratio relative to the telmisartan (see instant claims 1 and 6-12) that are made by their spray drying or granulating methods (see instant claims 14-15). While this modified reference does not describe the resulting tablet matrix as "dissolving", it has the same components instantly claimed as the constituents of a dissolving matrix which are water soluble components that are also capable of fast dissolution in physiological aqueous medium as required. Thus the tablet of Ambuhl et al. in view of Hauel et al. meets the limitations of a dissolving matrix. Therefore claims 1, 6-9, 11-12, and 14-15 are obvious over Ambuhl et al. in view of Hauel et al.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ambuhl et al. in view of Hauel et al. as applied to claims 1, 6-9, 11-12, and 14-15 above, and further in view of Gaviraghi (previously cited) and Ohkouchi (previously cited).

Ambuhl et al. in view of Hauel et al. make obvious the pharmaceutical composition of instant claim 1. In addition, Hauel et al. teaches the inclusion of additional active agents in with their compounds that include hydrochlorothiazide (HCTZ), a diuretic (see page 53 paragraph 2). Ambuhl et al. in view of Hauel et al. do not explicitly teach a bilayered configuration for the actives or a particular matrix for the HCTZ.

Gaviraghi teach a bilayered tablet configuration that includes telmisartan in one layer and another drug in the second layer (see page 13 lines 1-2). It is further taught that the telmisartan layer is formulated as taught in EP 0502314, which is also published as Hauel et al. (see page 11 lines 21-22).

Ohkouchi et al. teach disintegrating solid dosage forms (see abstract). In particular, HCTZ is an envisioned active for these compositions (see column 5 line 36).

It would have been obvious to one of ordinary skill in the art at the time of the invention to follow the suggestion of Hauel et al. and include HCTZ in the telmisartan containing tablets of Ambuhl et al. in view of Hauel et al. because of their explicit directive to couple HCTZ with their benzamidazole compounds and to achieve the diuretic properties known to be beneficial in the hypertension treatment provided by telmisartan dosing. As a known arrangement for telmisartan and another active within a single dosage form, it would have been obvious to one of ordinary skill in the art at the time of the invention to configure the tablet of Ambuhl et al. in view of Hauel et al. as a bilayered tablet with telmisartan and HCTZ in the separate layers. This would also allow one of ordinary skill in the art to separately control the rate of release for each of the

drugs. Given the teachings of Ohkouchi et al. regarding matrices known for the delivery of HCTZ, it also would have been obvious to utilize their matrix for the HCTZ layer in the bilayered tablet of Ambuhl et al. in view of Hauel et al. and Gaviraghi. Therefore claim 13 is obvious over Ambuhl et al. in view of Hauel et al., Gaviraghi, and Ohkouchi et al.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Applicants' admission filed July 18, 2011 in view of Straub et al. (US PGPub No. 2002/0019431).

According to applicants' admission, compositions substantially as detailed in example 4 in US PGPub No. 2005/0089575 were sold prior to the critical date and qualify as a prior sale under 35 USC 102(b). Two formulations are taught in this example where one (henceforth referenced as tablet A) has 40 mg of telmisartan in a bilayered tablet with the first layer composed of telmisartan at 16.7%, sorbitol (water soluble diluent) at 70%, sodium hydroxide (basic agent) along with meglumine (basic agent) at a molar ratio of 1:1.875 telmisartan to total basic agent, povidone at 5%, and excipient making up the balance. A second layer is composed of a diuretic in a matrix that is described in the reference as disintegrating (see paragraph 36). This bilayer tablet formulation does not include polyoxamer in the telmisartan layer.

Straub et al. teach that povidone and polyoxamers both act as wetting agents in a solid oral formulation and serve to facilitate water ingress in order to aid in dissolution (see paragraphs 30-31 and 59). Three varieties of polyoxamer are taught that include

Pluronic® F68 which is also known as poloxamer 188 (see paragraph 31). Poloxamer 188 meets the molecular weight requirement for the polyoxamer.

It would have been obvious to one of ordinary skill in the art at the time of the invention to exchange Pluronic® F68 for the povidone in the telmisartan layer of tablet A as the simple substitution of one known element for another to yield a predictable result. This modification yields a tablet layer composed as detailed in instant claim 1 as required by instant claim 13. While this modified reference does not describe the resulting telmisartan tablet matrix as "dissolving", it has the same components instantly claimed as the constituents of a dissolving matrix which are water soluble components that are also capable of fast dissolution in physiological aqueous medium as required. Thus the telmisartan layer of tablet A in view of Straub et al. meets limitations of a dissolving matrix. Therefore claim 13 is obvious over Applicants' admission filed July 18, 2011 in view of Straub et al.

***Response to Arguments***

Applicants' arguments filed July 18, 2011 have been fully considered but are unpersuasive.

Applicants argue that the absence of a teaching concerning the presence of a basic agent in Ambuhl et al. is an indication that such a component should be avoided. The silence of a reference about the presence of a particular component is not a teaching away from including such a component. Ambuhl et al. do not have any

teachings that explicitly exclude basic agents or direct the artisan of ordinary skill away from including them in the composition. As applicants note, the description of Ambuhl et al. is quite detailed, but this level of detail is not an indication that all possible options for components that could reasonably be utilized in the composition without deviating from the intent are explicitly named. Applicants additionally argue that the inclusion of a basic agent in a liquid preparation of Hauel et al. is not applicable to the tablet preparations of Ambuhl et al. Several tablet preparation methods taught by Ambuhl et al. employ a solution of the poorly water soluble drug. Since telmisartan is known to be solubilized by a strong base and meglumine is shown by Hauel et al. to act in this capacity (e.g. solubilizing telmisartan), it would have been obvious to include meglumine in a telmisartan containing composition of Ambuhl et al. to facilitate the preparation of the tablet form.

Applicants further argue that Hauel et al. do not teach why the meglumine is included with the telmisartan. The artisan of ordinary skill is not limited to the explicit statements of the prior art but are also equipped with their own scientific reasoning and logic. Telmisartan is well known as a poorly water soluble drug and Hauel et al. seek to generate an aqueous solution of telmisartan during the course of preparing their formulation. The inclusion of meglumine allows telmisartan to be solubilized and this drug was well known to be soluble in strong base. Therefore the artisan of ordinary skill would have known that the meglumine is being used to aid in solubilizing the telmisartan.

Applicants additionally argue that Ambuhl et al. would not have been combined with Hauel et al. because the former is concerned with compositions for cyclosporin. In addition to teaching cyclosporin as the poorly water soluble drug in their composition, Ambuhl et al. explicitly teach that other poorly water soluble drugs can be substituted for the cyclosporin to obtain equivalent compositions (see paragraphs 202 and 212). Hauel et al. teach telmisartan as one particular poorly water soluble drug; therefore their teachings would have been reasonable to combine with those of Ambuhl et al. to guide the selection of poorly water soluble drugs other than cyclosporine. These explicit teachings by Ambuhl et al. are in direct contract to applicants' suggestion that the teachings of Ambuhl et al. are only suitable for cyclosporin.

Applicants' remaining arguments reiterate those presented against the rejection made over Ambuhl et al. in view of Hauel et al. These arguments were addressed above and are similarly reiterated.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CARALYNNE HELM whose telephone number is (571)270-3506. The examiner can normally be reached on Monday through Friday 9-5 (EDT).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on 571-272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Caralynne Helm/
Examiner, Art Unit 1615

/Juliet C Switzer/
Primary Examiner, Art Unit 1634